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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
12/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/580,567	NAKAMURA ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *1-31 and 38-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/6/06 and 6/26/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-43 are all the pending claims for this application.

2. Claims 21-24, 32, and 34-43 were amended in the Reply of 9/2/08.

Election/Restrictions

3. Applicant's election without traverse of Group VI (Claims 32-37) in the reply filed on 9/2/08 is acknowledged.

4. Claims 1-31 and 38-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/2/08.

5. Claims 32-37 are all the claims under examination.

Information Disclosure Statement

6. The listing of references in the specification on p. 4 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

7. The IDS' of 10/6/06 and 6/26/07 have been considered and entered. Reference AA in the IDS of 10/6/06 has been stricken on the 1449 form because it was cited in the

PTO 892 form of 7/30/08 and the information is cumulative under 37 CFR 1.56(b). An initialed and signed copy of each IDS is attached.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 32-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 32-37 are indefinite for the recitation "Dlk" because the *original* claims do not define which protein is intended by the term. According to Kim et al. (J. Biol. Chem. 279(28):29478-29484 (2004)) "Dlk" is the dual leucine zipper-bearing kinase (DLK)) expressed in FaO rat hepatoma cells. However, the specification defines "Dlk" to mean "Dlk/Pref-1", which if correctly interpreted through incorporation by reference to the documents cited on p. 4 of the specification, would mean "delta-like protein".

Clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

9. Claims 32-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a) what the specification teaches for treating an animal subject with liver carcinoma in vivo or a human liver cancer animal model in vivo with anti-dlk (Delta-like protein) antibody therapy comprising the anti-human Dlk antibody clone 4C4 or 31C4; and

b) what the prior art discloses in the way of antibody therapies (Laborda (see section 10 below); Laborda (see section 11 below); and Padigaru (see section 12 below)),

does not reasonably provide enablement for the instant method of treating any dlk-expressing cancer in any subject, in vivo, including a human with just any anti-dlk antibody in order to provide an anticancer effect mediated by complement (CDC or ACC). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 32- 37 are broadly interpreted as being drawn to a method for treating any dlk-expressing cancer in a cancer-bearing subject such as an animal using an anti-cancer effective amount of an anti-dlk antibody (Claim 32) and the method of Claim 32 where the cancer cells are liver cancer cells (Claim 33) and the liver cancer cells are hepatocellular carcinoma and/or cholangiocellular carcinoma cells (Claim 34), and where the antibody is monoclonal (Claim 35), and where the cancer cells are human cancer cells and the antibody is an anti-human Dlk antibody (Claim 36), and the antibody mediates the anti-cancer effect by ACC (Claim 37).

The relative skill in the art required to practice the invention is a clinical oncologist with a background in immunotherapy.

Disclosure in the Specification

The specification teaches generally an anti-Dlk antibody exerts anticancer activity at least in the presence of complement. Since complement is contained in the blood of a patient, the anti-Dlk antibody functions as a therapeutic drug for a liver cancer. "In the Examples, although ADCC activity of the anti-human Dlk monoclonal antibody against the cells of human liver cancer cell line was not observed, this is presumably because that the Fc regions of the antibodies were derived from rat. Since CDC activity is observed, it is thought that ADCC will also be exerted if the Fc region is replaced with that of human" [0037].

In the working Examples of the specification, Applicants have demonstrated the following:

Example 1: the generation of three stable hybridoma clones (clones 1C1, 4C4 and 31C4) producing anti-human dlk antibodies; and detecting expression of human dlk protein in liver cancer from hepatocellular carcinoma tissue and cholangiocellular carcinoma tissue using the anti-human Dlk monoclonal antibody clone 1C1;

Example 2: the CDC activity on the HEK293(hdlk) cells when the anti-human Dlk antibody (clone 4C4 or 31C4) was added to a level of 0.2, 1.0 or 5 .mu.g/ml) was examined (FIG. 8B, Table 3.2). By measuring the CDC activity three days after the beginning of the culturing by MTT assay, it was confirmed that the number of live HEK293(hdlk) cells decreased in a dose-dependent manner of anti-human Dlk antibody, and that the activity of 31C4 was higher than that of 4C4.

Clone PC14 cells of the Huh-7(hDlk) cell line derived from human liver cancer stably expressing human Dlk were subcutaneously transplanted to nude mice and the tumor formation was compared with the case where the control cells (Huh-7 EGFP) were transplanted and drastic growth of the tumor was observed when compared with the control cells (FIG. 12B).

Applicants have identified three anti-human dlk antibodies, and only two of which were tested in the CDC assay, in vitro, and where one antibody outperformed the other. Applicants have not shown that any of their three monoclonals much less any other art-recognized anti-dlk antibody, could cause an anticancer effect on *any* cancer cell lines in vitro. Applicants have not shown that any of their three monoclonals much less any other art-recognized anti-dlk antibody could exert an anticancer effect through complement fixation (CDC or ACC) for any human cancer in an animal model. Applicants' specification has addressed the role of a dlk-expressing human liver cancer cell line in promoting tumor progression in vivo and the use of anti-dlk antibody reagents as a possible therapeutic modality based on in vitro CDC-killing of human liver cancer target cells with two antibody clones. The specification is not enabling for treating any cancer much less any cancer in human cancer patient with the antibody reagents developed by Applicants absent a further showing by a preponderance of the evidence.

Prior Art Status: treatment of some dlk-expressing cancers in an animal model with anti-dlk antibody therapy is predictable

Prior to Applicants application filing date, the field of art recognized dlk or "Delta-like protein" as a potential therapeutic target in some cancers with limited use of antibody-based immunotherapy.

Both Laborda (see section 10 below) and Laborda (see section 11 below) teach a therapeutic application of anti-Dlk monoclonal antibodies comprising administration of anti-Dlk immunotoxins to an animal. Conjugation of an anti-Dlk monoclonal antibody to a toxin, such as Psuedomonas exotoxin or other toxins commonly conjugated to an antibody are administered to an individual to target and selectively kill dlk-expressing cells present in SCLC, pheochromocytoma and neuroblastoma tumors. Laborda teaches full length anti-dlk antibodies which would otherwise comprise an Fc portion and which mediates ACC.

Padigaru (see section 12 below) teach that dlk is more highly expressed in liver and kidney tumors than in the corresponding matched normal tissue. Thus, expression of this gene could be used to differentiate between these samples and other samples on this panel and as a marker for these cancers. This expression in kidney and liver cancers is in agreement with published reports that Dlkl may be invovled in the cells response to growth and differentiation signals. Therefore, therapeutic targeting of this gene product with a human monoclonal antibody is anticipated to limit or block the extent of tumor cell growth and metastasis, particularly in kidney and liver tumors.

Prior Art Status: Translation of immunotherapeutics from In vitro to In vivo is unpredictable and requires undue experimentation

A tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and access of antibodies to the tumor cells are not evenly distributed and this is an important source of heterogeneity in tumor response to immunotherapeutics. Therefore, prediction of antibody effects in any cancer model much less a human subject is not reliable and further evaluation in animal tumor systems is essential.

In vivo animal drug testing *may be* a platform technology in a determination of enablement, but the complexity and difficulty of drug delivery for cancer treatment is underscored by Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)). Voskoglou-Nomikos conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis

or immune-response modulating agents" and "New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006)) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar.

Cespdes et al. (Clin. Transl. Oncol. 8(5):318-329 (2006)) review the some of the examples of art-recognized animal disease model correlates for the corresponding human disease in Tables 1-3. Cespedes emphasizes the challenges in using animal models as predictive correlates for human responsiveness to therapeutics and sets forth on pp. 318-319 a list of criteria that would represent the ideal in vivo model for studying cancer therapeutics. As regards the use of xenograft modeling, Cespedes teaches:

> "One limitation of the xenograft models is precisely their use of an immunocompromised host, which eliminates the possibility of studying the

role of the immune system in tumor progression. Some authors also think that cancer and host cells being from different species may limit the occurrence of critical tumor-stroma interactions, leading to an inefficient signaling. The organ of implantation could also become a limitation to the system. Thus, as it has already been described, subcutaneous xenografts infrequently metastasize and are unable to predict response to drugs" (p. 325, Col. 1, ¶2).

In another review of animal model testing from 2007, Talmadge et al. (Am. J. Pathol 170(3):793-804 (2007)) teach "Indeed primary human tumor xenografts can be predictive of clinical cytotoxic therapy for a given tumor histiotype provided that clinically relevant pharmacological dosing parameters are used. It is noted that human tumor cell lines in contrast to human primary tumor cells have generally been cultured for years losing much of their heterogeneity. This has resulted in undifferentiated tumors lacking the histology and cellular architecture characteristic of the modeled human tumor" (p. 795, Col. 2, ¶2)...and "xenograft tumor models can effectively predict responsive tumor histiotypes; however these models need to incorporate a pharmacological and toxicological foundation to be successful. In addition, animal models can be used to resolve a specific experimental question that can be appropriately translated into clinical trials" (p. 800, Col. 1, ¶2). "In addition to a quantitative determination of anti-tumor activity, responsive preclinical tumor models cane also be used to assess preliminary ADME (adsorption, distribution, metabolism and excretion) information and toxicity" (p. 800, Col, 2, ¶1). Talmadge states that "Before clinical testing, a new drug or drug

formulation should demonstrate safety and/or efficacy profile compared with current therapeutics in animal models. The comparison should incorporate rigorous animal models and not be based on highly responsive models, such as ones with rapid outcome that are convenient or with which the investigator is familiar. Furthermore, tumor and animal models should meet specific biological criteria including heterogeneity, appropriate histology, metastatic propensity, and appropriate genetic criteria depending on the targeted drug metabolism, limited immunogenicity, and potential etiology. Last, the model should have the potential to provide a correlation between therapeutic model outcome and clinical activity, optimally with previous documentation of relevance between mice and humans" (p. 800, Col. 2, ¶3).

One skilled in the art would reasonably conclude that further additional and undue experimentation is required to establish that the breadth of scope for the instant claimed methods is fully enabled, namely, a showing that any dlk-expressing cancer in any cancer subject, and even a human, could be treated with any anti-dlk antibody, where the method endpoint of tumor killing by CDC/ACC was accomplished by the antibody anticancer activity.

Prior Art Status: the use of just any anti-dlk antibody that mediates CDC/ACC whether in vitro or in vivo is unpredictable

The broadest claims of the method do not characterize the features of the anti-Dlk antibody- only that it binds Dlk expressed on the surface of a cancer cell and that it mediate *any* anticancer action on the cancer cell. Thus the claims could encompass any antibody isotype, and fragments of those antibodies, also which are void of the Fc

portion(s). The potential scope of antibodies exceeds what Applicants claims actually enabled fo, especially Claim 37, where the anticancer effect must occur in the presence of complement. Thus, in order for this to occur, the antibody would need to be of a preferred isotype and possess the Fc domain.

At least according to Salfeld (Nat. Biotech. 25(12):1369-1372 (2007)), the properties for the IgG isotype constant regions shown in Table 1 differ based on the intended effector function(s). Salfeld teaches on p. 1371, Col. 1 that:

"Antibodies designed for selective eradication of cancer cells typically require an active isotype that permits complement activation and effector-mediated cell killing by antibody-dependent cell-mediated cellular cytotoxicity. Although IgG1 and IgG3 both meet these criteria (Table 1), IgG3 has not been used for therapeutic antibody development probably because of a somewhat shorter half life, susceptibility of the longer hinge region to proteolysis, and extensive allotypic polymorphism."

Thus the ordinary artisan would reasonably conclude that the specification is not enabling for the breadth of anti-Dlk antibodies having any anticancer activity much less one mediated through complement.

In view of insufficient working examples in the specification and the field of art at time of application filing for treating any cancer with any anti-Dlk antibody in any subject in vivo much less a human, the ordinary artisan could not predict which antibody could be used against which Dlk-expressing cancer absent further detailed and undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 32, 35 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Laborda (USPN 5580738; published December 3, 1996).

Claims 32, 35 and 37 are broadly interpreted as being drawn to a method for treating any dlk-expressing cancer in a cancer-bearing subject such as an animal using an anti-cancer effective amount of an anti-dlk antibody (Claim 32) where the antibody is

monoclonal (Claim 35) and the antibody mediates the anti-cancer effect by ACC (Claim 37). The requirement that the antibody mediate ACC would exclude antibody fragments missing the Fc portion.

Laborda discloses a therapeutic application of anti-Dlk monoclonal antibodies comprising administration of anti-Dlk immunotoxins to an animal. Conjugation of an anti-Dlk monoclonal antibody to a toxin, such as Psuedomonas exotoxin or other toxins commonly conjugated to an antibody are administered to an individual to target and selectively kill dlk-expressing cells present in SCLC, pheochromocytoma and neuroblastoma tumors. Laborda teaches full length anti-dlk antibodies which would otherwise comprise an Fc portion and which mediates ACC. The claims are not limited to the kind of cancer expressing the dlk protein, and therefore, Laborda anticipates the invention.

11. Claims 32, 35 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Laborda (EP 1013762; published 6/28/00; cited in the IDS of 6/26/07).

The interpretation of Claims 32, 35 and 37 is discussed above under section 10.

Laborda discloses a therapeutic application of anti-Dlk monoclonal antibodies comprising administration of anti-Dlk immunotoxins to an animal. Conjugation of an anti-Dlk monoclonal antibody to a toxin, such as Psuedomonas exotoxin or other toxins commonly conjugated to an antibody are administered to an individual to target and selectively kill dlk-expressing cells present in SCLC, pheochromocytoma and neuroblastoma tumors [0020, 0054]. Laborda teaches full length anti-dlk antibodies

which would otherwise comprise an Fc portion and which mediates ACC. The claims are not limited to the kind of cancer expressing the dlk protein, and therefore, Laborda anticipates the invention.

12. Claims 32-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Padigaru et al. (WO 02/081635; published 10/17/02; filed 4/3/02; cited in the IDS of 10/6/06) as evidenced by Salfeld (Nat. Biotech. 25(12):1369-1372 (2007)) and as evidenced by Jin et al. (Expert. Opin. Biol. Ther. 8(4):371-377 (2008) Abstract).

The interpretation of Claims 32, 35 and 37 is discussed above under section 10. Claims 33, 34 and 36 are interpreted as being drawn to the method of Claim 32 where the cancer cells are liver cancer cells (Claim 33) and the liver cancer cells are hepatocellular carcinoma and/or cholangiocellular carcinoma cells (Claim 34), and where the cancer cells are human cancer cells and the antibody is an anti-human Dlk antibody (Claim 36).

Padigaru discloses a gene called NOV11a that is defined as being the same as human Dlk "delta-like protein" in Example 11 (pp. 120-124). In Table 11D Genseq results show 99% identity with human Dlk and in Table 11E BLASTP results for human Dlk of 99% identity. On pp. 282-296, the expression analysis of NOV11a in human tissues is analyzed. In Table LC . Panel 1.3D (bottom right of table) on p. 284, NOV11 expression is compared between liver, fetal liver and liver carcinoma (hepatoblast) and is shown to be expressed in the carcinoma sample but at a lower level than fetal liver, whereas normal liver does not express NOV11a. In Table LD. Panel 2D (upper right of

table) on p. 288, NOV11a expression is compared between normal liver and liver cancer. In 2/5 liver cancer samples, NOV11a is expressed and it is not expressed in 2/2 samples.

Padigaru at lines 24-29 on p. 294 states:

"There are also high levels of expression of this gene in a liver cancer cell line. In addition, low but significant expression of this gene is associated with lung and CNS cancer. Earlier DLK1 gene has been shown to be differentially expressed in small cell lung carcinoma and neuroendocrine tumor cell line (Ref.3). Therefore, therapeutic modulation of this gene, through the use of small molecule drugs, or antibodies could be of benefit in the treatment of liver, lung and CNS cancers."

Padigaru at lines 13-15 on p. 295 incorporates Laborda et al (J. Biol. Chem. 268:3817-3820 (1993); cited in the IDS of 10/6/06) as a general reference on the dlk protein.

Padigaru at lines 16-24 on p. 295 states:

"In addition, this gene is more highly expressed in liver and kidney tumors than in the corresponding matched normal tissue. Thus, expression of this gene could be used to differentiate between these samples and other samples on this panel and as a marker for these cancers. This expression in kidney and liver cancers is in agreement with published reports that Dlkl may be invovled in the cells response to growth and differentiation signals. Therefore, therapeutic targeting of this gene product with a human monoclonal antibody is anticipated to limit or block the extent of tumor cell growth and metastasis, particularly in kidney and liver tumors."

Padigaru at line 29 on p. 295 states:

"This gene codes for delta like protein precursor (DLK), belonging to NOTCH family."

Padigaru discloses methods for treating cancers on pp. 78-82, and more specifically antibody therapeutics on pp. 44-45, and where the antibodies generated against NOV11a protein, for example, are full length comprising an Fc portion for

mediating ACC as evidenced by Salfeld (see Table 1 under "effector functions" for C1) and where Padigaru discloses monoclonal (pp. 31-41) and human antibodies (pp. 36-38).

Padigaru does not specifically disclose that NOV11a was identified in liver cancer of the cholangiocellular carcinoma cell type but as evidenced by Jin (abstract), Dlk expression is observed in, and therefore inherent to, cholangiocellular carcinoma cells.

The claimed method invention is anticipated by the cited references.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Partial Signatory Authority